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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/834,321	04/13/2001	Jeffrey V. Ravetch	TRU-0005	2584

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EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 01/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/834,321	RAVETCH, JEFFREY V.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3 and 5-22* is/are pending in the application.

4a) Of the above claim(s) *3,5-9 and 16-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,10-15 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 January 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/07/03 has been entered.

Claims 1, 3, 5-22 are pending

Claims 3, 5-9 and 16-21 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

Claims 1, 10-15 and 22 drawn to a method for enhancing cytotoxicity with an antibody, wherein the antibody are specific for a HER2/neu growth factor receptor or for CD20 B cell antigen are under consideration in the instant application.

In view of the amendment, filed 10/07/03 the following rejections remain:

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 10-15 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention for the same reasons set forth in the previous Office Action, mailed 4/09/03

Applicant's arguments, filed 10/07/03), have been fully considered, but have not been found convincing.

Applicant asserts that: (i) the specification supports the invention of claim 1 without the limitation that antibody binding to activating receptors FcγRIIA and Rcγ RIIIA, and pointed to pages 6 and 14 of the Specification as filed to support said statement; (ii) the operability of the method of claim 1 is also supported by the Example 1, wherein FcγRIIB deficient mice exhibited a profound enhancement of the cytotoxic activity; (iii) the examiner has misjudged the unpredictability of the relevant art as well as the amount of guidance in the specification and the amount of experimentation required to practice the invention. The present Specification provides ample guidance and it was routine in the art at the filing date as to how to modify the Fc portion of an antibody and thereafter screen modified antibodies for the desired properties.

Contrary to Applicant's assertions, after careful examination of the passages pointed by the Applicant the Examiner failed to find the support for the statement that therapeutic antibody, recited in claim 1 does not required to retained , maintained or enhanced binding affinity for activating receptors FcγRIIA and Rcγ RIIIA. Moreover, Applicant clearly stated that to practice the invention it would be essential that antibodies, while reducing their binding affinity for FcRIIB , due to modification of the Fc portion of the antibody , still retaining or enhancing binding to FcRIIA and FcRIIIA (page 7, lines 10-15 of specification as filed). The Example 1 demonstated that inhibitory FcγRIIB was a factor in determining the in vivo anti-tumor activity of mAb TA99 2 (see page 33, lines 1-6 in particular). There is no disclosure in the Example 1 that said antibody do not binding to FcRIIA or FcRIIIA . Moreover, it is noted that in Example 1, FcγRIIB deficient mice, i.e. mice lacking FcγRIIB was used. The amended claim 1 recited a method for enhancing cytotoxicity by therapeutic antibody, which method comprises disrupting activation of SHIP by FcγRIIB caused by binding of the antibody to said receptor. It is not clear how the example using the mice lacking said receptor support the operability of the method that required the presence and activity of said receptor? Moreover, Pearse et al., newly cited (Pearse et al., Immunol., 1999, Vol.10, pages 753-760) teach that interpretation of data obtained on mice deficient in FcγRIIB is complicated, since animals deficient in the inhibitory receptors have different responses compare to control ones (see entire document, page 756 in particular).

With regards to the issue that the examiner has misjudged the unpredictability of the relevant art and that it was routine in the art at the filing date as to how to modify the Fc portion of an antibody and thereafter screen modified antibodies for the desired properties. .

Contrary to Applicants assertion, the instant fact pattern fails to indicate that representative number of structurally related compounds, i.e. the genus of antibodies that have a reduced binding affinity for FcRIIB , due to modification of the Fc portion of the antibody , while retaining or enhancing binding to FcRIIA and Fc RIIIA the artisan would not know the identity of a reasonable number of representative compounds falling within the scope of the instant claims and consequently would not know how to make them. An assay for *finding* a product is not equivalent to a positive recitation of *how to make* a product.

It is the examiner position that the specification does not provide sufficient guidance and examples as to which modifications would be acceptable to retain these specific structural and functional properties of claimed antibodies to be used in the claimed method for enhancing cytotoxicity elicited by antibody *in vivo,* which method comprises disrupting activation of SHIP by FcRIIB. In addition, the term "modifying" encompass any substitution, deletion or insertion (page 14, lines 13-16 of Specification as filed) of Fc portion of the antibody that will affect their structural and functional properties. Applicant acknowledges that single amino acid replacement in Fc portion of the mouse anti-HER2 antibody 4D5 reduces affinity for **both** FcRII and FcRIII receptors (page 35, lines 5-20 of the Specification as filed). The references cited by the examiner indicated that protein chemistry is probably one of the most unpredictable areas of biotechnology and that it is known in the art that even single amino acid changes or differences in a proteins amino acid sequence can have dramatic effects on the protein's function.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method for enhancing cytotoxicity elicited by a therapeutic antibody *in vivo*, which method comprises disrupting activation of SHIP by Fc RIIB in manner reasonably correlated with the scope of the claims. *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, lack of working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

4. Claims 1, 10-15 and 22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action, , mailed 4/09/03

Applicant's arguments, filed 10/07/03), have been fully considered, but have not been found convincing.

Applicant asserts that the specification provides experimental evidence that cytotoxicity of a therapeutic antibody is enhanced by modifying the Fc portion such that it has reduced affinity for FcγRII as compared to an unmodified antibody. The specification teach how to identify antibody and provides at least two assays by which to test for cytotoxicity.

Contrary to applicant assertion, it is the examiner position that the claims as written encompass the genus of antibodies that have a reduced binding affinity for FcRIIB , due to modification of the Fc portion of the antibody , while retaining or enhancing binding to FcRIIA and Fc RIIIA that can be used in a method for enhancing cytotoxicity elicited by a this antibody *in vivo*, which method comprises disrupting activation of SHIP by Fc RIIB .

However, there does not appear to be an adequate written description in the specification as-filed how to make an antibody that have a reduced binding affinity for FcRIIB , due to modification of the Fc portion of the antibody , while retaining or enhancing binding to FcRIIA and Fc RIIIA and use them in a method for enhancing cytotoxicity elicited by antibody *in vivo,* which method comprises disrupting activation of SH2 domain containing inositol 5-phosphatase (SHIP) by FcRIIB . A description of what a material does rather than of what it is, usually does not suffice. The patent does not more than describe the desired function of the compound called for and contains no information by which a person of ordinary skill in the art would understand that the inventors possessed the claimed invention. At best, it simply indicates that one should run tests on a wide spectrum of compounds in the hope that at least one of them will work. Inadequate written description that merely identifies a plan to accomplish an intended result "is an attempt to preempt the future before it has arrived" *Fiers v. Revel*, 984 F.2d 1164,1171 9Fed.Cir. 1993).

The Examiner notes that the claimed invention which is drawn to a genus of antibodies may be adequately described if there is a (1) sufficient description of a representative number of species, or (2) by disclosure of relevant, identifying characteristics sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. To satisfy the disclosure of a "representative number of species" will depend on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. "Relevant, identifying characteristics" include structure or other physical and /or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of such identifying characteristics sufficient to show the applicant was in possession of the claimed genus. (see Revised Guidelines for the Examination of Patent Applications Under the 35 U.S.C.112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No.4, pages 1099-1111, Friday January 5, 2001).

In the instant case, however, there is no described or art-recognized correlation or relationship between the structure of the invention, modified antibody, that reduced binding affinity for FcRIIB , due to modification of the Fc portion of the antibody , while retaining or enhancing binding to FcRIIA and Fc RIIIA that can be used in a method for enhancing cytotoxicity elicited by a this antibody *in vivo*, which method comprises disrupting activation of SHIP by Fc RIIB, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed method for enhancing cytotoxicity with an

antibody, wherein the antibody are specific for a HER2/neu growth factor receptor or for CD20 B cell antigen.

5. No claim is allowed

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/ 272-0840 The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/ 272-0841 . Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is 703/872-9306

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January 26, 2004

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